Heart Failure: State of the Art 2015

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Co-Chief, UCLA Division of Cardiology

Learning Objectives

- Outline the prevalence, risk factors for, diagnosis and prognosis with heart failure
- Describe current evidence-based guideline recommendations for heart failure therapy
- Describe the impact of medical therapies on heart failure patient outcomes
- Highlight the benefits of device therapy and disease management for heart failure

Heart Failure Background

- Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures
- Major cost-driver of HF is high incidence of hospitalizations
- Despite treatment advances large number of eligible patients are not receiving one or more evidence-based HF therapies

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Hospital Discharges</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>5,700,000</td>
<td>870,000</td>
<td>50% at 5 years</td>
<td>1,023,000</td>
<td>$30.7 billion</td>
</tr>
</tbody>
</table>

Survival after the onset of congestive heart failure in Framingham Heart Study subjects

Prognosis with Heart Failure

- Overall 5-year mortality 50%
- Hospitalized Patients 1-year mortality:
  - Mild to Moderate Symptoms: 10-20%
  - Severe Symptoms: 40-60%
Outcomes During and After HF Hospitalization

- In-hospital
  - Length of stay (mean) 6.2 days
  - Mortality rate 4.1%
- Hospital readmissions
  - 20% at 30 days
  - 50% at 6 months
- Longer-term mortality
  - 11.6% at 30 days
  - 33.1% at 12 months


Approach to the Classification of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk for developing heart failure (HF)</td>
</tr>
</tbody>
</table>
  - Hypertension
  - CAD
  - Diabetes mellitus
  - Family history of cardiomyopathy
| B     | Asymptomatic HF |
  - Previous MI
  - LV systolic dysfunction
  - Asymptomatic valvular disease
| C     | Symptomatic HF |
  - Known structural heart disease
  - Shortness of breath and fatigue
  - Reduced exercise tolerance
| D     | Refractory end-stage HF |
  - Method: symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

Definition of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart Failure with Reduced Ejection Fraction (HFREF)</td>
<td>≤ 40%</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFREF and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>2. Heart Failure with Preserved Ejection Fraction (HFPEF)</td>
<td>≥ 50%</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFPEF. The diagnosis of HFPEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFPEF, Borderline</td>
<td>41% to 49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HFREF.</td>
</tr>
<tr>
<td>b. HFPEF, Improved</td>
<td>&gt;40%</td>
<td>It has been recognized that a subset of patients with HFPEF previously had HFREF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>

Heart Failure Pathophysiology

Myocardial injury ➔ Fall in LV performance ➔ Activation of RAAS, SNS, ET, and others ➔ Myocardial toxicity ➔ ANP, BNP ➔ Peripheral vasoconstriction ➔ Hemodynamic alterations ➔ Remodeling and progressive worsening of LV function ➔ Morbidity and mortality ➔ Heart failure symptoms

Pathophysiologic Effects of Angiotensin II and Epinephrine/Norepinephrine

Cardiac Myocyte
  - Hypertrophy
  - Apoptosis
  - Cell Stiffening
  - Increased Wall Stress
  - Increased O2 Consumption
  - Impaired Relaxation
Fibroblast
  - Hyperplasia
  - Collagen Synthesis
  - Fibrosis
Peripheral Artery
  - Vasostenosis
  - Endothelial Dysfunction
  - Hyperplasia
  - Decreased Compliance
Coronary Artery
  - Vasostenosis
  - Endothelial Dysfunction
  - Atherosclerosis
  - Restenosis
  - Thrombosis

ACC/AHA HF Guidelines:
Management of Heart Failure (Stage C)

Life Prolonging Medical Therapy
- ACE inhibitors or ARB (Class I, evidence A) all patients without contraindications or intolerance
- β-Blockers (Class I, evidence A) all patients without contraindications or intolerance
- Aldosterone antagonists (Class I, evidence A) all patients with Class II-IV HF without contraindications or intolerance, when close monitoring can be assured


Effect of ACE Inhibitors on Mortality
and Hospitalizations in Patients with HF

32 Trials of ACEI in Heart Failure. ACEI (n = 3870). Placebo (n = 3235)
Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273:1450-1459

Total Mortality Death or Hospitalization CHF Hospitalization

OR 0.77 (0.67-0.88) p<0.001

Survival Rates in Patients Receiving ACE Inhibitors Across NYHA Classes

Consequences
PRAISE
PROMISE
SOLVD-P
SOLVD-T
DIG
V-HeFT

ValHeFT: ARB added to Standard HF Care Including ACEI

Mortality

Probability of Survival (%)

Placebo
Valsartan

P< 0.001

Months since Randomization


CHARM-Alternative

Primary outcome of CV death or CHF hospitalization

Placebo
Candesartan

Proportion wih CV Death or CHF Hospitalization (%)

HR 0.77 (95% CI 0.67-0.89), P= .0004
Adjusted HR 0.70, P<.0001

Number at risk
Candesartan 1,013 929 831 434 122
Placebo 1,015 887 798 437 126

**ACEI/ARB in Heart Failure**

- Indicated for all patients with asymptomatic LV dysfunction and for Class I to IV heart failure. (Contraindications: hyperkalemia, angioedema, pregnancy)
- Titrate to target doses (example enalapril 10 mg bid, lisinopril 20 qd, ramipril 10 mg qd, benazepril 40 qd, valsartan 160 mg bid, candesartan 32 mg qd)
- Monitor serum potassium and renal function. Advise checking chemistry panel 1-2 weeks after first dose.
- Use of ACE inhibitor together with ARB reserved as a consideration only in patients not candidates for aldosterone antagonist.

**Effects of Aldosterone**

- Cardiac Myocyte
  - Hypertrophy
  - Hyperplasia
- Fibroblast
  - Collagen Synthesis
  - Fibrosis
- Peripheral Artery
  - Vasoconstriction
  - Endothelial Dysfunction
  - Hypertrophy
  - Decreased Compliance
- Kidney
  - Potassium Loss
  - Sodium Retention

**RALES: Aldosterone Antagonist Reduces All-Cause Mortality in Chronic HF**

- Spironolactone (25 mg) + standard care (n = 822)
- Placebo + standard care (n = 841)

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<thead>
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<th>Months</th>
<th>Probability of Survival (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>0.95</td>
</tr>
<tr>
<td>6</td>
<td>0.90</td>
</tr>
<tr>
<td>9</td>
<td>0.85</td>
</tr>
<tr>
<td>12</td>
<td>0.80</td>
</tr>
<tr>
<td>15</td>
<td>0.75</td>
</tr>
<tr>
<td>18</td>
<td>0.70</td>
</tr>
<tr>
<td>21</td>
<td>0.65</td>
</tr>
<tr>
<td>24</td>
<td>0.60</td>
</tr>
<tr>
<td>27</td>
<td>0.55</td>
</tr>
<tr>
<td>30</td>
<td>0.50</td>
</tr>
<tr>
<td>33</td>
<td>0.45</td>
</tr>
<tr>
<td>36</td>
<td>0.40</td>
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HR = 0.70 (95% CI, 0.60 to 0.82)
P < 0.001

*Ejection fraction ≤ 35% Class III or IV symptoms at some point in prior 2 months.

**Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms: EMPHASIS HF**

- HR = 0.63 (0.54-0.74), p < 0.001

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<th>No. at Risk</th>
<th>Years from Randomization</th>
<th>Placebo</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1373</td>
<td>0</td>
<td>1364</td>
<td>356</td>
</tr>
<tr>
<td>1364</td>
<td>1</td>
<td>925</td>
<td>512</td>
</tr>
<tr>
<td>925</td>
<td>2</td>
<td>562</td>
<td>232</td>
</tr>
<tr>
<td>562</td>
<td>3</td>
<td>199</td>
<td>232</td>
</tr>
</tbody>
</table>

**Aldosterone Antagonists in Heart Failure**

- Indicated for patients with mild, moderate, or severe HF due to LVD (LVEF < 0.40). (Contraindications: hyperkalemia, Cr > 2.5 in men and > 2.0 in women)
- Spironolactone 12.5 mg PO qd starting dose (or 6.25 mg in higher risk patients) or Eplerenone 25 mg qd (or 12.5 mg in higher risk patients). Decrease potassium supplementation and loop diuretic dose at time of initiation.
- Critical to very closely monitor serum potassium and renal function. Advise checking chemistry panel at 72 hours, 1 week, and 4 weeks.
- Advance Spironolactone dose at 4 weeks to 25 mg PO qd or Eplerenone 50 mg which is the target dose. Avoid higher doses due to risk of hyperkalemia.

**The Use of Beta Adrenergic Blocking Agents in Heart Failure**

- Initial hemodynamic deterioration followed by reverse remodeling (decrease in EDV and ESV) with improved ventricular function over time (increased LVEF)
Major Trials of β-Blockade in Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Follow-up</th>
<th>NYHA Class</th>
<th>LVEF (%)</th>
<th>Effects on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS</td>
<td>641</td>
<td>1.9 yrs</td>
<td>II-III</td>
<td>&lt; 35</td>
<td>All-cause mortality: ↓ 22%, NS</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>2647</td>
<td>1.3 yrs</td>
<td>II-III</td>
<td>&lt; 35</td>
<td>All-cause mortality: ↓ 34% (P=0.001)</td>
</tr>
<tr>
<td>MDC</td>
<td>383</td>
<td>1 yr</td>
<td>II-III</td>
<td>&lt; 40</td>
<td>Death or need for transplant: ↓ 30%, P=0.05</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>3991</td>
<td>1 yr</td>
<td>II-III</td>
<td>&lt; 40</td>
<td>All-cause mortality: ↓ 34% (P=0.002)</td>
</tr>
<tr>
<td>US Carvedilol</td>
<td>1094</td>
<td>7.5 months</td>
<td>II-III</td>
<td>&lt; 35</td>
<td>All-cause mortality: ↓ 22% (NS)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>10.5 months</td>
<td>IV</td>
<td>&lt; 25</td>
<td>All-cause mortality: ↓ 30% (NS)</td>
</tr>
</tbody>
</table>


Early Benefits and Early Safety of Carvedilol in Severe HF: COPERNICUS

**Early Mortality Reduction**
- Placebo: 11.4% (P=0.008)
- Carvedilol: 15.7% (P=0.05)

**Lower Risk for Worsening CHF**
- Placebo: 2.3%
- Carvedilol: 1.7%

**Weeks After Randomization**
- Placebo: 2%
- Carvedilol: 4%

**Events (%)**
- Placebo: 3%
- Carvedilol: 2%

**Risk Reduction**
- Placebo: 4%
- Carvedilol: 10%

**Event rates: Placebo 2.3%; Carvedilol 1.7%**

Effects of Sympathetic Activation in Heart Failure

- CNS sympathetic outflow
- Cardiac sympathetic activity
- Sympathetic activity to kidneys
- Activation of RAS
- Sodium retention
- Myocyte death
- Increased arrhythmias
- Vasoconstriction
- Disease progression

Not All β-Blockers Reduce Mortality in HF

**BEST**
- Bisoprolol: 10%
- Bucindolol: 10%
- Carvedilol: 12%
- Metoprolol: 10%
- Nebivolol: 10%
- Xamoterol: 10%

**SENIORS**
- Bisoprolol: 10%
- Bucindolol: 10%
- Carvedilol: 10%
- Metoprolol: 10%
- Nebivolol: 10%
- Xamoterol: 10%

β-Blockers Differ in Their Long-Term Effects on Mortality in HF

- Bisoprolol: Beneficial
- Bucindolol: Beneficial
- Carvedilol: Beneficial
- Metoprolol: No effect
- Metoprolol: Not well studied
- Nebivolol: Beneficial
- Nebivolol: No effect
- Xamoterol: Harmful

**References:**
**COMET: Effect Carvedilol vs Metoprolol Tartrate on Mortality in HF**

- **Risk Reduction**
  - Metoprolol Tartrate: ↓17% (7%, 26%) P=0.0017
  - Carvedilol: ↓17% (7%, 26%) P=0.0017

- Extrapolation from the survival curves suggested that carvedilol extended median survival by 1.4 years as compared with metoprolol tartrate.

- Metoprolol mean dose: 85 mg QD; Carvedilol mean dose: 42 mg QD.

**COMET did not evaluate metoprolol succinate, the agent used in the MERIT-HF Trial.**

**Mortality Rates:**
- Metoprolol: 40%
- Carvedilol: 34%

**Beta Blocker Therapy in Heart Failure**
- Indicated for all patients with asymptomatic LVD dysfunction and for Class I to IV Heart Failure with LVEF < 0.40
- Contraindications: cardiogenic shock, severe reactive airway disease, 2/3rd degree HB
- Use one of the 3 evidence-based beta blockers in HF: eg carvedilol, metoprolol succinate, bisoprolol
- Start at very low HF doses and up-titrate to target doses at two week intervals, or highest dose short of target dose that is well tolerated
- Monitor HR and BP

**Neurohormonal Activation as the Therapeutic Target in Heart Failure**

- **Therapies with Demonstrated Benefit in Clinical Trials**
  - Sympathetic Nervous System
    - Beta Adrenergic Blockers
  - Renin Angiotensin Aldosterone System
    - Angiotensin Converting Enzyme Inhibitors
      - (Angiotensin II Receptor Antagonists)
    - Aldosterone Antagonists

**GISSI HF: All-cause Mortality**

- Adjusted HR (95% CI): 0.91 (0.833 – 0.998) P value 0.041
- **NNT = 56**
- **ARR = 1.8%**

**Ivabradine and Outcomes in Chronic Heart Failure (SHIFT)**

- **SHIFT: Hazard ratios for primary and individual outcomes, ivabradine vs placebo groups**
  - **CV death or HF hospitalization**
    - **Ivabradine, n=3241 (%)**
    - **Placebo, n=3264 (%)**
    - **HR (95% CI)**
    - **p**
    - 24 vs 29 0.82 (0.75 - 0.90) <0.001
  - **Death from heart failure**
    - 3 vs 5 0.74 (0.58 - 0.94) 0.014
  - **HF hospitalization**
    - 16 vs 21 0.74 (0.66 - 0.83) <0.0001
  - **CV death, HF hospitalization, or admission for nonfatal MI**
    - 25 vs 30 0.82 (0.74 - 0.89) <0.001

The benefit of ivabradine appeared to go up with increasing heart rate (HR<77 HR 0.93; HR ≥77 HR 0.75)

**AhFT: Trial Summary**

- **Fixed-dose HYD/ISDN**
- **Placebo**
- **Hazard ratio=0.57**
- **P=0.01**

**African Americans with Class III to IV HF, LVEF 24%, on ACEI, BB, AA**

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

- Endogenous vasoactive peptides (natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)
- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention

inactive metabolites

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

- Patients at Risk
  - LCZ696 (n=4212)
  - Enalapril (n=4187)

- Kaplan-Meier Estimate of Cumulative Rates (%)
  - LCZ696: 1117
  - Enalapril: 914

- HR = 0.80 (0.73-0.87)
- P = 0.000002
- Number needed to treat = 21

PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

- LCZ696 was more effective than enalapril in . . .
  - Reducing the risk of CV death and HF hospitalization
  - Reducing the risk of CV death by incremental 20%
  - Reducing the risk of HF hospitalization by incremental 21%
  - Reducing all-cause mortality by incremental 16%
  - Incrementally improving symptoms and physical limitations

- LCZ696 was better tolerated than enalapril . . .
  - Less likely to cause cough, hyperkalemia or renal impairment
  - Less likely to be discontinued due to an adverse event
  - More hypotension, but no increase in discontinuations
  - Not more likely to cause serious angioedema

Effect of Digoxin on Mortality in Heart Failure: The Digitalis Investigation Group

- Relative Risk: 0.99
- 95% CI: 0.91–1.07
- P = .80

Diuretic Therapy in Chronic Heart Failure

- Loop diuretics are mainstay of therapy for CHF (Given to > 85% of patients)

- Beneficial effects of diuretic therapy:
  - ↓ Dyspnea and other congestive symptoms
  - ↓ Volume overload
  - Facilitate successful initiation and titration of ACE inhibitors, β-blockers, vasodilators

- No outcome studies of diuretic therapy in chronic HF and effects on morbidity and mortality unknown

Pharmacological Therapy for Management of Stage C HFαEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional supplements as treatment for HF are not recommended in HF-βEF</td>
<td>III: No Benefit</td>
<td>B</td>
</tr>
<tr>
<td>Hormonal therapies other than to replete deficiencies are not recommended in HF-βEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
<tr>
<td>Drugs known to adversely affect the clinical status of patients with HF-βEF are potentially harmful and should be avoided or withdrawn</td>
<td>III: Harm</td>
<td>B</td>
</tr>
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<td>Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation</td>
<td>III: Harm</td>
<td>C</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocking drugs are not recommended as routine in HF-βEF</td>
<td>III: No Benefit</td>
<td>A</td>
</tr>
</tbody>
</table>

Cardiac Resynchronization Therapy for Heart Failure

- In patients with heart failure 27 to 53% of patients have IVCDs (RBBB, LBBB, IVCD)
- Abnormal conduction contributes to abnormal ventricular activation/contraction and subsequent dysynchrony between the RV and LV
  - Reduced systolic performance
  - Mechanical inefficiency
  - Worsened prognosis

Abnormal conduction contributes to abnormal ventricular activation/contraction and subsequent dysynchrony between the RV and LV
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Cardiac Resynchronization Therapy: Weight of Evidence

- >8,000 patients evaluated in randomized controlled trials
- Consistent improvement in quality of life, functional status, and exercise capacity
- Strong evidence of reverse remodeling
  - ↓ LV volumes and dimensions
  - ↑ LVEF
  - ↓ Mitral regurgitation
- Reduction in HF and all-cause morbidity and mortality


CARE-HF: Effect of CRT Without an ICD on All-Cause Mortality

- HR: 0.64 (95% CI: 0.48-0.85)
- P=.0019

CARE-HF: Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>OMT (n=404)</th>
<th>CRT + OMT (n=409)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death + CV Hospitalization</td>
<td>225 (55%)</td>
<td>159 (39%)</td>
<td>0.63 (.51 to .77)</td>
<td>&lt;.001</td>
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<tr>
<td>CV Hospitalization</td>
<td>184 (46%)</td>
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<td>0.61 (.49 to .77)</td>
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<td>HF Hospitalization</td>
<td>133 (33%)</td>
<td>72 (18%)</td>
<td>0.48 (.36 to .64)</td>
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<td>All-Cause Death</td>
<td>120 (30%)</td>
<td>82 (20%)</td>
<td>0.64 (.48 to .85)</td>
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OMT=optimal medical therapy

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CARE-HF: Clinical Outcomes

ScD-HeFT and Other ICD Device Trials in HF

- HF Etiology
  - Ischemic: 100%
  - Non-ischemic: 100%
- NYHA Class
  - I/II/III (35%/35%/30%)
  - III/IV (87%/13%)
- LVEF < 30%
  - < 35%
- No. Pts
  - MADIT II: 458
  - COMPANION: 458
  - DEFINITE: 2521
  - SCD-HeFT: 1520
- Follow-Up
  - MADIT II: 20 months
  - COMPANION: 12 months
  - DEFINITE: 24 months
  - SCD-HeFT: 45 months
- Hazard Ratio
  - MADIT II: 0.69
  - COMPANION: 0.64
  - DEFINITE: 0.66
  - SCD-HeFT: 0.77


Important Comorbidities in Heart Failure

- Cardiovascular
  - Hypertension
  - Coronary artery disease
  - Peripheral vascular disease
  - Cerebral vascular disease
  - Hyperlipidemia
  - Atrial fibrillation
- Non-Cardiovascular
  - Obesity
  - Diabetes
  - Anemia
  - Chronic kidney disease
  - Thyroid disease
  - COPD / Asthma
  - Smoking
  - Sleep disordered breathing
  - Liver disease
  - Arthritis
  - Cancer
  - Depression

Patient Education is Essential in HF

Patient Instructions

- Monitor daily weights
- Salt restricted diet (e.g. 2-3 gm sodium diet)
- Medications, need for adherence
- Activity Rx
- Smoking Cessation Advice/Counseling
- What to do if HF symptoms worsen
- Close follow-up and monitoring


Heart Failure with Preserved Ejection Fraction

Treatment of patients with predominantly diastolic dysfunction heart failure has not been well studied.

Control hypertension

Diuretics should be used cautiously, at low dose initially, recognizing that the stiff heart is highly dependent on adequate preload.

Rate control for atrial fibrillation

ACE inhibitors, calcium channel blockers, and beta blockers have favorable effects upon hemodynamics but their impact on longer term outcome is not known.


Evidence-Based, Guideline-Recommended Heart Failure Reduced Ejection Fraction Therapies

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>Relative Risk Reduction in Mortality</th>
<th>Number Needed to Treat for Mortality (standardized to 36 months)</th>
<th>NNT for Mortality</th>
<th>Relative Risk Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17%</td>
<td>35</td>
<td>39</td>
<td>31%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>9</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>30%</td>
<td>9</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>43%</td>
<td>5</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>CRT</td>
<td>36%</td>
<td>12</td>
<td>8</td>
<td>52%</td>
</tr>
<tr>
<td>ICD</td>
<td>23%</td>
<td>14</td>
<td>23</td>
<td>NA</td>
</tr>
</tbody>
</table>


Potential Impact of Optimal Implementation of Evidence-Based HF Therapies on Mortality

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>Guideline Patient Population Eligible for Treatment, n</th>
<th>Current HF Population Eligible and Untreated, n (%</th>
<th>Potential Lives Saved per Year</th>
<th>Potential Lives Saved per Year (Sensitivity Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>2,459,644</td>
<td>501,767 (20.4)</td>
<td>6516</td>
<td>(3336-11,260)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2,512,560</td>
<td>361,809 (14.4)</td>
<td>12,922</td>
<td>(6166-22,329)</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>603,014</td>
<td>385,326 (63.9)</td>
<td>21,407</td>
<td>(10,960-36,695)</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>150,754</td>
<td>139,749 (92.7)</td>
<td>6655</td>
<td>(3407-11,500)</td>
</tr>
<tr>
<td>CRT</td>
<td>326,151</td>
<td>196,604 (61.2)</td>
<td>8317</td>
<td>(4258-14,372)</td>
</tr>
<tr>
<td>ICD</td>
<td>1,725,732</td>
<td>852,112 (49.4)</td>
<td>12,179</td>
<td>(6238-21,045)</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>-</td>
<td>67,996</td>
<td>(34,813-117,497)</td>
</tr>
</tbody>
</table>

Cumulative Impact of Clinical Trial Evidence Based Heart Failure Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Relative-risk</th>
<th>2 yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>35%</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>↓ 23%</td>
<td>27%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>↓ 35%</td>
<td>18%</td>
</tr>
<tr>
<td>Aldosterone Ant</td>
<td>↓ 30%</td>
<td>13%</td>
</tr>
<tr>
<td>CRT-D (EF&lt;35, QRS&gt;120)</td>
<td>↓ 36%</td>
<td>8%</td>
</tr>
<tr>
<td>Omega-3 FA</td>
<td>↓ 9%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction if all five therapies are used: 80%
Absolute risk reduction: 28%, NNT = 4

Adapted from Fonarow GC. Rev Cardiovasc Med. 2006;7:S3-11

Heart Failure Prevention

Patients at risk for heart failure:
- Treat systolic and diastolic hypertension according to guidelines
- Treat diabetes according to guidelines
- Treat atherosclerosis according to guidelines
- Treat lipid disorders according to guidelines
- Encourage smoking cessation
- Encourage exercise
- Discourage heavy alcohol intake, illicit drug use
- Consider ACEI/ARB and beta blocker use in those at risk for HF


Advances in the Treatment of HF

- Increased attention to prevention
- ACEI / β-blocker / aldosterone antagonist combination established as the “cornerstone” of therapy
- Evidence that β-blockers’ effects are not homogeneous
- Downgrade in recommendation for use of digoxin
- Integration of CRT and ICD device therapy into the standard therapeutic regimen
- Recognition that “special populations” of HF patients may benefit from or require different approaches
- New strategies to improve utilization of evidence based therapies


The Approach to Heart Failure

- The economic burden of HF continues to grow and HF is one of the single most expensive and deadly health care problems
- Medical therapies and nonpharmacologic measures for HF that can impact patients’ need for re-hospitalization, costs of care, and survival are underutilized in conventional practice settings
- Every efforts should be made to implement evidence-based HF therapies when indicated and optimize care of HF